REMARKS/ARGUMENTS

The Status of the Claims.

Claims 34 to 45, 47 to 55 and 63 to 69 are pending with entry of this amendment. Claims 68 and 69 are added herein. Claims 34, 35, 44, 53 and 66 are amended herein. These amendments introduce no new matter and support is replete throughout the specification. These amendments are made without prejudice and are not to be construed as abandonment of the previously claimed subject matter or agreement with any objection or rejection of record.

With respect to claim 34, the amendment removes the objected conservative variant term. The 90% identity aspect and functional RS-tRNA pair interactions can be found throughout the specification. For example, see specification at paragraphs 22, 70, 140, 143 and 172; the title; and in Figure 1. Support for the aspect of binding and aminoacylation of tRNA of SEQ ID NO: 3 by O-RSs; or aminoacylation of O-tRNAs by RSs of SEQ ID NO: 2 can be found throughout the specification, e.g., at paragraphs 38, 70, 110, 130, 131, 142 and 179; the section starting at paragraph 133, the Examples, and in Figures 1 and 5.

Amendment of claim 35 merely removes a redundant term.

Amendment of claim 44 removes an objected term.

The amendment to claim 47 corrects antecedent reference in light of the amendment to the parent claim.

The amendment to claim 53 merely deletes an aspect already present in the parent claim.

The amendment to claim 66 removes a redundant aspect, as requested by the Office.

New claims 68 and 69 are supported at paragraphs 70 and 140, Figure 1, and the sequence listing.

Applicants submit that no new matter has been added to the application by way of the above Amendment. Accordingly, entry of the Amendment is respectfully requested.

35 U.S.C. §112, First Paragraph.

Claims 34 to 55 and 62 to 67 were rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement. To the extent the rejection is deemed applicable to the amended claims, Applicants traverse. Applicants stand by their remarks of the previous Response, which are only the more reasonable in light of current amendments.

To be an enabling disclosure under § 112, first paragraph, a patent must contain a description that enables one skilled in the art to make and use the claimed invention. That some experimentation is necessary does not constitute a lack of enablement; the amount of experimentation, however, must not be unduly extensive. *See In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Whether undue experimentation is required by one skilled in the art is typically determined by reference to eight factors considered relevant to the inquiry: (1) quantity of experimentation necessary; (2) amount of guidance presented; (3) presence of working examples; (4) nature of the invention; (5) state of the prior art; (6) relative skill of those in the art; (7) predictability of the art; and (8) breadth of the claims. *See id.*

As a preliminary matter, Applicants note that in a related case (11/016,348, based on essentially the same specification), Examiner Leavitt and SPE Woitach have acknowledged that 90% identity is reasonable for the given O-RS and O-tRNA in light of the skill in the protein engineering art and the structural functional information provided in the specification. That is, one of skill can alter a substantial number of residues while retaining structures and active sites, without undue experimentation, with a reasonable expectation of success in providing adequate function. However, it has been noted that enablement further requires that modified O-RSs and O-tRNAs should properly interact with each other. Given this concern of the Office, Applicants have amended the claims to require continued functional interaction of certain modified components with given reference components. For example, if the O-RS is modified to have less than 100% identity with SEQ ID NO: 2, the modified O-RS retains structures functionally interacting with the original reference tRNA of SEQ ID NO: 3, thereby providing a reasonable expectation the modified O-RS will functionally interact with a closely related O-tRNA having limited modifications. The

present independent claim 34 is amended to incorporates this aspect, enhancing the expectation of success in practicing the method of the claim.

Many of the following remarks were present in the Response of March 23, 2009, but are reiterated for the record with regard to the presently amended claims. Applicants appreciate the extensive Response to Arguments section provided in the prior Action. However, in light of the present amendments, the claims should now be deemed to be of reasonable scope.

In the previous Response, Applicants had noted that the general structures and functions of synthetases and tRNAs are well known. In the Response to Arguments, at page 7, the Office argues that the knowledge of tRNA structure "does not provide sufficient guidance for the twenty one cognate aminoacyl-tRNA synthetase-suppressor tRNA pairs to be used in site-specific incorporation of amino acid analogs into proteins in prokaryotes and eukaryotes." This statement does not alter the fact that it would be reasonably easy for one of skill to, e.g., modify arms to change complimentary residue pairs (e.g., G-C to C-G), without destroying activity and specificity (as agreed with regard to the sister case). The present claims are directed to O-muTrpRSs limited to require certain key sequences and preferably aminoacylating certain identified O-tRNAs. The claims and specification teach RS/tRNA pairs that are likely to be successful. The specification does not teach one of skill to embark in a random survey of unrelated synthetases. Contrary to the argument in the rejection, the guidance in the specification directs one of skill to efficient identification of active species and not down the suggested relatively unproductive path of examining 21 cognate synthetases.

The cited statement at page 7 does not contradict the unarguable fact of high general knowledge of RS and tRNA structures and functions. Therefore, it can not be argued that *Wands* factors favor finding a lack of enablement for limited variations of the provided method components. The quantity of experimentation would be low because one of skill can easily identify any number of modifications outside the required structures that should be expected to retain activity. The nature of the invention and state of the prior art are such that the specific inventions could have been practiced, including limited modifications, without undue experimentation. The high skill in the art allowed one to of such skill could have

practiced the present claims. The currently claimed methods could predictably have been practiced with a reasonable expectation of success applying a reasonable effort.

Bridging pages 7 and 8, the Office suggests undue experimentation is required to practice the previous claims because "there is no supporting evidence to substantiate a reasonable correlation of how any aminoacyl-tRNA synthetase aminoacylates the corresponding suppressor tRNA and no other endogenous tRNA in the cell, or how a suppressor tRNA is not aminoacylated by any of the endogenous [synthetases] in a method that specifically incorporates a 5-substituted tryptophan unnatural amino acid in any host system (e.g., prokaryote or eukaryote)?" Emphasis added. The present claims address certain issues here. In other aspects, the rationale for arguing against enablement is faulty. As a preliminary matter, Applicants have noted that the MPEP and relevant case law do not require Applicants to explain how their inventions work. The "how" of the universe has been incompletely explained by mankind; science and technology largely provide correlative models of observed structure-function relationships. Identification of a structure-function relationship does not require one to identify how the structure functions, only that the structure correlates with function. Here, the original specification teaches synthetase structures observed to correlate with aminoacylation of identified O-tRNAs and not with endogenous tRNAs. For example, the specification identifies general RS and tRNA structures provided by mutations at key identified positions correlated to the stated function. The general structures with specific function-correlated modifications are taught in the specification and presented in the current claims. Applicants note that the claims are not directed to the universe of any host system (e.g., prokaryote or eukaryote) but are directed to specifically taught functional eukaryotic systems. The RS/tRNA pairs are specifically structured to functionally interact in a eukaryotic system (e.g., with the tRNA pseudo A box, and 5' flanking sequences - see paragraphs 140 and 172) to incorporate 5-substituted tryptophans (e.g., with specific mutations such as Pro144 - see paragraph 179). It is clear that one of skill in the art, understanding the general structures of a RS/tRNA pair, with guidance of the many structures identified as correlating with functional activity would be able to incorporate a 5-substituted tryptophan in a eukaryote without undue experimentation (while, possibly not fully understanding how it all worked).

Previous claims were found unpredictable at page 8 because Applicants had noted surprise at specification paragraphs 178 and 179 "that a single mutation at the active site of BsTrpRs completely altered its specificity from L-tryptophan to 5-HTPP." The Office offered that "[t]his result further underlines the unpredictability" of active site substitutions. Surprise is when something happens different from expectations. As previously noted, the general expectation in the art is that substitutions, particularly conservative substitutions, often do not completely abrogate activity. It is the exception to the rule that causes surprise, the surprise does not set the rule. In any case, the surprise (novel and non-obvious) aspect is included in the claims and provides guidance to observed functionally interacting structures for those in the art wishing to practice the claimed inventions.

It is worth noting, now that Applicants have taught the functional structures, there is a reasonable expectation that they will function across the range of 5-substituted unnatural amino acids. In Deiters (JACS 125:11782 to 11783; 2003) 4 of 5 O-RSs negatively selected not to charge a natural amino acid and positively selected to charge para-substituted phenylalanine were able to charge both an azide para-substituted and an acetylene para-substituted phenylalanine. In this analogous situation, it is reasonable to expect the RS/tRNA pairs of the invention could suppress with intelligently selected para-substituted tryptophan.

At the bottom of page 8, the Office continues the argument that there is "[n]o disclosure of other" O-RS and O-tRNA species. However, enablement can be adequate where functioning species have been identified along with structures correlated with the desired function and interaction. As incorporated in presently amended claims, and as discussed above.

At pages 9 and 10 of the Action, the Office is not persuaded by the fact that one of skill can start with the given functional sequences and easily identify additional functional species as previously claimed. The Office acknowledges that one of skill can envision the variant sequences, but such a high proportion would be inactive as to render experimentation undue to identify functional embodiments. However, as the Office often points out: one of skill can use their "common sense". Although there are a multitude of mutations that could reduce an enzyme's activity, one of skill would have a good sense of

changes likely to change activity, or not. Further, because the present specification and claims identify structures correlated to function, one of skill would know to avoid drastic (e.g., non-conservative) modifications of these structures. Modifications of key identified structures are outside the scope of the claims. One of skill would not waste time pursing, e.g., theoretical RS-tRNA pair sequences that attack the general physical structure, modifications expected to substantially change the shape or charge or the active site, or modifications expected to attack structures identified as correlating to function in the present specification. By avoiding bad experimental design, one of skill can practice the claimed inventions without undue experimentation.

In summary, *Wands* factors support a finding of enablement for the currently amended claims. Because the current claims are directed to, e.g., the specifically enabled combination of O-RSs having particular functional interaction correlated structures, paired with O-tRNAs having particular structures favoring functional interaction with the O-RSs to incorporate reasonably limited unnatural amino acids, it would not require undue experimentation to practice methods across the new scope of the claims.

CONCLUSION

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the claims are deemed not to be in condition for allowance after consideration of this Response, a telephone interview with the Examiner is hereby requested. Please telephone the undersigned at (510) 769-3510 to schedule an interview.

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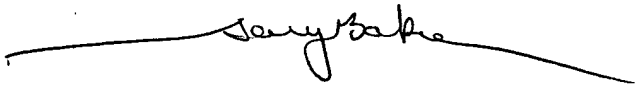
Respectfully submitted,



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